Attachment

Declaration under 37 C.F.R. § 1.132 by Dr. Peter Jarrett

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Pratt et al.		
SERIAL NUMBER:	10/723,626	EXAMINER:	ALSTRUM ACEVEDO, James Henry
FILING DATE:	November 26, 2003	ART UNIT:	1616
FOR:	BUOYANT POLYMER PARTICLES FOR DELIVERY OF THERAPEUTIC AGENTS TO THE CENTRAL NERVOUS SYSTEM		

Boston, Massachusetts

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION of PETER JARRETT UNDER 37 C.F.R. §1.132

I, PETER JARRETT, PH.D., DO HEREBY DECLARE:

1. I am the Chief Technology Officer of Ocular Therapeutix, Inc., a company developing bioresorbable hydrogels for ocular therapies. Previously, I was the Vice President Biomaterials R&D at Genzyme, Inc. and before that Vice President R&D at Focal, Inc. At these positions, I directed all phases of pre-clinical, clinical and commercial product development, including design, manufacture, and administration of new polymeric-based product material.

I have over 30 years of experience in the development of drugs, biomaterials and drug delivery systems. I have an in-depth understanding of the total development process including project management, clinical trials, regulatory, formulation, drug delivery, QC and manufacturing scale-up. I have worked extensively in a variety of projects directed at slow release and controlled release of proteins and other drugs from polymeric systems.

I hold a Ph.D. in polymer science, and I have authored over 32 papers, book chapters and abstracts. I am listed as an inventor on over 30 patents principally in the area of drug formulations, drug delivery, and biomaterials.

2. I have recently reviewed United States Patent Application number 10/723,626 ("the '626 application"), which is entitled "BUOYANT POLYMER PARTICLES FOR DELIVERY OF THERAPEUTIC AGENTS TO THE CENTRAL NERVOUS SYSTEM," and which was filed in the United States Patent and Trademark Office (USPTO) on November 26, 2003.

3. I understand that the '626 application has been assigned to seaCoast NeuroScience, Inc. I am not employed by seaCoast, nor do I hold stock in seaCoast at the present time.

4. I have been informed that claims 22-31 and 39-52 of the '626 application are currently undergoing examination by the USPTO. I have reviewed these claims, and I understand that the claims relate to a method for administering a therapeutic agent within the central nervous system of a subject using polymer particles that contain a therapeutic agent and a buoyancy agent. Examples of therapeutic agents and buoyancy agents are provided in the '626 application.

5. I have been informed that the examiner who is examining the '626 application at the USPTO has rejected claims 22-30, 40-44, and 48-52 as obvious over U.S. Patent No. 5,560,933 to Soon-Shiong et al. ("the Soon-Shiong patent"). I have recently reviewed the Examiner's arguments supporting this rejection as set forth in the Office Action dated May 11, 2009. I have also recently reviewed the Soon-Shiong patent.

6. In my opinion, the invention described by the claims of the '626 application is not one that would have been obvious, at the time the '626 application was filed, based on the Soon-Shiong patent.

7. The Soon-Shiong patent is directed primarily to compositions and methods for *in vivo* delivery of substantially water insoluble pharmacologically active agents, where the active agent is delivered in a soluble form or in the form of suspended particles.

The Soon-Shiong patent also describes a process for manufacturing a composition for *in vivo* delivery. In the process, sonication is used "to disperse a dispersing agent containing dissolved or suspended pharmacologically active agent into an aqueous solution of a biocompatible polymer... whereby a shell of crosslinked polymer is formed around fine droplets of non-aqueous medium" (see col. 4, lines 50-55 of the Soon-Shiong patent). Vegetable oil is provided as an example of a dispersing agent for suspending or dissolving the substantially water insoluble pharmacologically active agent (see col. 6, lines 47-56 of the Soon-Shiong patent).

8. The Soon-Shiong patent therefore uses a dispersing agent (i.e., vegetable oil) during the *manufacturing* process in order to ease the manufacturing of compositions with non-soluble drugs by *suspending* or *dissolving* water insoluble drugs.

In contrast, the '626 application describes the use of agents such as vegetable oil in order to affect the behaviour of pharmaceutical formulations *in vivo* (i.e., not simply to affect the manufacturing process of the formulations).

9. The role of vegetable oil in the Soon-Shiong patent (i.e., as a dispersing agent) is significantly different from the role of buoyancy agents described in the '626 application. In fact, the term "suspend" (as in "suspended particles") as used in the Soon-Shiong patent is not related to buoyancy-type suspension at all, but rather refers only to chemically suspending (i.e.,

dispersing an insoluble material within a non-solvent, such as fat globules present in milk) pharmaceutical agents. The object of Soon-Shiong suspension is to prevent agglomeration or settling of the drug in the aqueous medium; thus forming a stabilized suspension. It is the polymeric shell, which consists of both hydrophilic and hydrophobic molecular domains, that provides the stabilization of the suspension by presenting a hydrophilic surface to the aqueous medium. The modification of hydrophobic particles to impart a hydrophilic surface is a commonly employed strategy for stabilizing a suspension.

In contrast, the meaning of the term "suspend" that is relevant to the '626 application refers to the *spatial* location of particles within the CNS. For example, the particles may be suspended in the upper regions of the CNS.

10. The '626 application provides the definition: "as used herein, "controllably buoyant" means a polymer composition that comprises at least one buoyancy agent. The composition or amount of the buoyancy agent is adjusted to target it to or away from the brain or the spinal cord (the top or the bottom of the CNS)." The specific gravity of the composition is determined by the amount of the buoyancy agent incorporated into the composition *in addition to* the amounts and specific gravities of the other components of the composition. There is no suggestion in the Soon-Shiong patent that the exemplified materials would provide control over the specific gravity of the final particle composition.

The pharmaceutical formulations described in the Soon-Shiong patent are not expected to be controllably buoyant within the cerebrospinal fluid, nor would there be any expectation that such formulations could provide targeted delivery of a therapeutic agent to the CNS. The patent does not present any data or statements related to the specific gravity of the suspended particles, which is an additive property of the overall composition of the particle. In particular, the dispersing agents of the Soon-Shiong patent would not be expected to impart buoyancy control for the formulations when administered *in vivo*. In the Soon-Shiong patent, particles are specifically formulated to contain a polymeric shell and a pharmaceutically active agent within the shell. The active agent is completely contained within the polymeric shell, and the active agent may be in the form of a solid (i.e., one or more solid particles) or a liquid (e.g., dissolved in a solution). A suspending or dissolving agent such as vegetable oil may be present, for example, in the interface between the active agent and the polymeric shell, or in the solution containing the active agent that is surrounded by the polymeric shell. See col. 4, lines 14-28 and col. 6, line 47 to col. 7, line 50 in the Soon-Shiong patent. There is no attempt made in the Soon-Shiong patent to manipulate these formulation variables to control specific gravity or buoyancy, nor is there any speculation on this point.

The Soon-Shiong patent makes no mention of the mechanism or rate of biodegradation of the polymeric shell, other than that if it is made from a protein it is "degradable by proteolytic enzymes." In fact, modification of proteins and polymers as described in the Soon-Shiong patent may alter the degradation mechanism of the polymeric shell. If such a composition were to be delivered to the cerebrospinal fluid, active agent would be released if the polymeric shell were compromised or breached. The active agent would be released into the CSF either as a solid mass or as a liquid in solution. In the case of solid particles, the particles of active agent would move about in the CSF according to the density of the active agent. Alternatively, in the case of liquids, the liquid active agent would either disperse in the

CSF (if soluble) or coalesce into a separate liquid phase of active agent (if insoluble). In either case, the buoyancy of the active agent would be completely uncontrolled once the polymer shell is compromised. Targeted delivery via a buoyancy mechanism within the CSF may therefore be impossible using the particles disclosed in Soon-Shiong. Even if targeted delivery via a buoyancy mechanism were proved using the particles of Soon-Shiong, I would not have found such an application obvious from the disclosure of Soon-Shiong, nor would I have expected successful targeting within the CNS if such an application had been proposed.

11. The Soon-Shiong patent does not mention any other uses for dispersing agents that are relevant to the '626 application.

12. Substantial modifications would be necessary in order for the materials described in the Soon-Shiong patent to be capable of carrying out the method that is the subject of the '626 application, particularly the provision of targeted delivery of therapeutic agent within the CNS. Incorporation of vegetable oil as a buoyancy agent (rather than a suspension or dissolution agent) would require, for example, modification of the location and amount of the oil in the formulations. Suspension of insoluble agents, as reported in the Soon-Shiong patent, requires that the oil be localized between the active agent and the polymer shell. This arrangement, however, does not necessarily direct the active agent to be carried to the desired position within the CNS according to the buoyancy of the oil. The Soon-Shiong patent does not suggest modifying this arrangement in any way that would result in a composition that is controllably buoyant within the CSF.

13. The Examiner states that the Soon-Shiong patent exemplifies particles containing a buoyancy agent. However, the claims of the '626 application require more than just particles with a buoyancy agent – such particles must also be controllably buoyant within the CSF. In my opinion, the particles described in the Soon-Shiong patent would not be inherently controllably buoyant within the CSF. In addition, physical properties, such as specific gravity, that are inherent to a substance or composition do not make it obvious to use that substance in all ways that require that specific physical property. Otherwise, "method of use" claims could not be considered novel.

14. In consideration of the above, prior to November 26, 2003 I do not believe that it would have been obvious to use a dispersing agent such as vegetable oil to control the buoyancy of a microparticulate formulation in the CSF. Furthermore, even if I had desired a formulation that is controllably buoyant in the CSF, I would not have found it obvious to use the dispersing agents mentioned in the Soon-Shiong patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Nov. 10, 2009 Signed: _____

Peter Jarrett, Ph.D.

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